

Cancer Prone Disease Section

Short Communication

Peutz-Jeghers syndrome

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Abstract

Review on Peutz-Jeghers syndrome, with data on clinics, and the genes involved.

Identity

Other names

Hamartomatous Intestinal Polyposis

Polyps-and-Spots Syndrome

Note

Syndrome associating mucocutaneous melanotic pigmentation, intestinal polyposis, and an increased risk of cancers.

Inheritance

Autosomal dominant with a high penetrance; incidence rate of the disease ranges from 1 in 8,300 to 1 in 200,000; 1/3 to 1/2 of cases due to de novo mutations.

Clinics

Phenotype and clinics

Skin numerous brown or blueish mucocutaneous macules (melanin spots), especially around the orifices (mouth, including the buccal mucosa, eyes, nostrils, anus, genitalia), and digits; the skin hyperpigmentation may disappear with age, in puberty and adulthood. Note: in patients with isolated mucocutaneous melanotic pigmentation (without polyps), the cancer risk is lower, and the genetic defect seems different.

Gastrointestinal tract (GI tract): polyps of hamartomatous origin (with a characteristic arborization of nonstriated muscles) may be found in any portion of the GI tract with varying frequencies: from 95% to 15%: (small bowel, jejunum, ileum, large intestine, rectum, stomach, duodenum).

Intussusception and bleeding are common symptoms, which may be cause of death. the age of onset is variable from the first year of life onwards (median age of onset 10-25 yrs); polyps have also been reported in other organs (renal pelvis, urinary bladder, ureters, lungs, nares, gallbladder).

Neoplastic risk

Tumors develop, with a relative risk of 10-20, and a cumulative risk of more than 90% between ages 15 and 64 yrs (Giardiello et al.,2000).

The mean interval between the diagnosis of PJS and the diagnosis of cancer is about 20 yrs (the mean age at the first cancer diagnosis about 41 yrs). The overall relative risk (RR) for cancer is greater in females than in males and greatest for gastrointestinal, pancreatic, and gynecologic-cervical cancers (Resta et al.,2013). In particular, the specific RR is:

small intestine: 520
stomach: 213
pancreas: 140
colon: 84
esophagus: 57
cervix: 55.6
ovary: 30

benign sex cord tumor with annular tubules in females or Sertoli cell tumors in males: 27
lung: 17
uterus: 16
breast: 15.2 (comparable to that of BRCA1 / BRCA2 mutations carriers - Hearle et al.,2006)

Treatment

Surveillance with endoscopic (GI tract) and gynecologic regular screenings, surgery when needed.

Evolution

Patients inherit mutations in one allele. The remaining allele is later inactivated generally by LOH or sometimes somatic mutation. This biallelic inactivation of STK11 leads to a loss of tumor suppressor activity, thereby promoting tumorigenesis.

Prognosis

The prognosis for individuals affected by PJS is thus mainly determined by the risk of malignancy. Although little information on prognosis is available, one report suggests that PJS-associated cancers are particularly aggressive (Spigelman et al.,1989). Several researches show that a diagnosis of PJS has great psychosocial impact, although the physical impact on the patient is not greater than that in the general population (Woo et al.,2009).

Genes involved and proteins

STK11 (LKB1) is the only gene in which mutations has been identified as causative of PJS, to date (Hemminki et al.,1998, Jenne et al.,1998). Evidence for genetic heterogeneity are described but no other locus has been clearly associated.

One child with a PJS hamartoma show a 19q13.4 translocation, however no pathogenic variants in candidate genes mapping to this breakpoint were identified (Hearle et al.,2004).

Between 25 patients with PJS without STK11 pathogenic mutations, one had a heterozygous pathogenic variant of MUTYH gene, common cause of autosomal recessive form of adenomatous polyposis (Alhopuro et al.,2008).

Moreover Wang et colleagues identified 2 germline variants which are represented in all six PJS samples analyzed and are independent of STK11 mutation (Wang et al.,2014).

STK11 (serine/threonine kinase 11)

Location

19p13.3

Note

A majority of PJS patients shows germline mutations in STK11 gene (around 80%-94%). However, the

identification of germline mutations in other genes suggests a genetic heterogeneity of PJS, no definitely known to date.

DNA/RNA

Description

9 coding exons, spanning 23 kb. (Additional non-coding exons are described). The gene is transcribed in telomere to centromere direction.

Transcription

9 transcripts; 4 protein coding.

Protein

Description

433 amino acids, 48.6 kDa; N-term with a nuclear localization domain and a putative cytoplasmic retention signal, a kinase domain, and a C-terminal CAAX box prenylation motif.

Expression

Ubiquitous, especially high expression in fetal liver and testis where it is required during spermiogenesis (Towler et al.,2008).

Localisation

Found in both the nucleus and the cytoplasm. Localization is thought to be dependent on interaction with proteins such as SMARCA4 (BRG1), STK11IP (LIP1), STRADA, CAB39 (MO25).

Function

Tumor suppressor serine/threonine-protein kinase that controls the activity of AMP-activated protein kinase (AMPK) family members, thereby playing a role in various processes such as cell metabolism, cell polarity, apoptosis and DNA damage response. Acts by phosphorylating the T-loop of AMPK family proteins, leading to promote their activity: phosphorylates PRKAA1 , PRKAA2 , BRSK1 , BRSK2 , MARK1 , MARK2 , MARK3 , MARK4 , NUA1 , NUA2 , SIK1 , SIK2 , SIK3 and SNRK but not MELK. Also phosphorylates non-AMPK family proteins such as STRADA and possibly p53/TP53. Acts as a key upstream regulator of AMPK by mediating phosphorylation and activation of AMPK catalytic subunits PRKAA1 and PRKAA2: it thereby regulates inhibition of signaling pathways that promote cell growth and proliferation when energy levels are low, glucose homeostasis in liver, activation of autophagy when cells undergo nutrient deprivation, B-cell differentiation in the germinal center in response to DNA damage. Also acts as a regulator of cellular polarity by remodeling the actin cytoskeleton. Required for cortical neurons polarization by mediating phosphorylation and activation of BRSK1 and BRSK2, leading to axon initiation and specification. Involved in DNA damage response: interacts with p53/TP53 and recruited to the CDKN1A/WAF1 promoter to participate in transcription activation. Able to

phosphorylate p53/TP53; the relevance of such result in vivo is however unclear and phosphorylation may be indirect and mediated by downstream STK11/LKB1 kinase NUAK1. Also acts as a mediator p53/TP53-dependent apoptosis via interaction with p53/TP53: translocates to mitochondrion during apoptosis and regulates p53/TP53-dependent apoptosis pathways (Karuman et al., 2001; Baas et al., 2003; Boudeau et al., 2003; Baas et al., 2004; Lizcano et al., 2004; Jaleel et al., 2005; Zeng et al., 2006; Hou et al., 2011).

Homology

Orthologs found in several species and include: *Xenopus laevis* egg and embryonic kinase 1 (XEEK1), *Caenorhabditis elegans* partitioning defective gene 4 (PAR4), mouse LKB1 and *Drosophila* LKB1.

Mutations

Germinal

Around 200 pathogenic mutations of STK11 gene has been reported to date, including missense, nonsense, splice site variants, small deletions, small insertions, small indels, large deletions, large insertions and complex rearrangements. Between them more than 90% are associated with PJS. In addition are described: one individual with a nonsense variant and diagnosis of gonadotropin-independent precocious puberty and one patient with a large insertion and diagnosis of juvenile polyposis syndrome.

Somatic

Many of the polyps that develop in PJS show loss of heterozygosity or second somatic mutation of STK11 gene. Somatic mutations rarely occur in sporadic tumors. However, somatic mutations of STK11 gene can be frequent revealed in lung adenocarcinoma (Matsumoto et al., 2007).

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